(b) incubating the nucleic acid components which allow for the specific annealing and linkage of the nucleic acid components to thereby produce the nucleic acid multicomponent construct.

REMARKS

Support for the amendments to claims can be found throughout the application (see, for example, page 7, lines 4-12; page 11, lines 7-8; and page 16, Table I).

Claim Rejections under 35 U.S.C. §112, 2nd paragraph

The Examiner has rejected claims 1-38 and 42 under 35 U.S.C. §112, 2nd paragraph. In particular, the Examiner has first rejected claims 1-30 and 42 as because "it is unclear...what....the nature of the interaction between the nucleic acid components and the 'separate nucleic acid components' (is)." Applicants have amended the claim to more precisely define the relationship between the nucleic acid components and the "separate nucleic acid components" by indicating that the "separate nucleic acid component" is "another (other than the first referenced "each") nucleic acid component of said at least two nucleic acid components." The skilled artisan would understand this language to indicate that each individual nucleic acid component provided by the method must bear at least one 5' or 3' single-stranded end which is complementary to a 5' or 3' end of at least one of the other nucleic acid components provided by the method. Furthermore, the claim has further been amended to clarify that the 5' or 3' single-stranded end of the nucleic acid component may be, rather than directly complementary to a 5' or 3' single-stranded end of another of the nucleic acid components, complementary to an adaptor molecule which in turn is also complementary to the 5' or 3' single-stranded end of another of the nucleic acid components.

The Examiner has further rejected claim 4 as vague and indefinite because "it is unclear if the flanking single stranded sequences are the same "single stranded 5' or 3' terminal sequence" as recited in the base claim. Accordingly, Applicants have amended the claim to clarify that this dependent claim adds the additional requirement that each nucleic acid component possess two, rather than at least one, single stranded 5' or 3' terminal sequence.

The Examiner has further rejected claims 1 and 11 as vague and indefinite because "it is unclear if the 'nucleic acid components', 'separate nucleic acid components' and 'adaptor molecules'

can be the same or must be distinct molecules. Applicants have amended claim 1 to clarify that the referred to "nucleic acid components" and "separate nucleic acid components" referred to in unamended claim 1 are meant to describe a relationship which each nucleic acid component must bear with one of the other nucleic acid components provided by the method. In addition, claim 1 has been amended as described above to clarify that includes methods by which one or more separate adaptor molecules are provided, which adaptor molecules provide the for the specific joining of 5' or 3' single-stranded ends of at least two of the nucleic acid components. Accordingly, the recitation of an "adaptor molecule" is meant to indicate a molecule that is distinct from a "nucleic acid component," but which bears complementarity to at least two of the nucleic acid components through their respective 5' or 3' single-stranded ends. Furthermore, dependent claim 11 has been amended to clarify that it encompasses methods of joining multiple nucleic acid components, as in claim 1, in which at least two of the nucleic acid components are joined by an adaptor molecule. This adaptor molecule, as indicated above for independent claim 1, is distinct from any of the nucleic acid components, and further has the property of providing terminal sequences that are complementary with 5' or 3' terminal sequences of the at least two nucleic acid components to be joined.

The Examiner has further rejected claims 17, 21 and 23 as "vague and indefinite because it is unclear...what....the modifications (claimed are)." Dependent claim 17, and claims 21 and 23 which depend from dependent claim 17, provide a further limitation to the method of claim 1 wherein at least one of the nucleic acid components of claim 1 is modified - either covalently or noncovalently. This claim has been amended to clarify the fact that covalent or noncovalent modification is to one (or more) of the nucleic acid components and need not pertain to each of the at least two nucleic acid components provided in claim 1. The Examiner, however, has rejected the claim as vague and indefinite, presumably because of a supposed uncertainty as to the scope of the phrase "covalently or non-covalently modified."

Applicants respectfully point out that, in determining the definiteness, the language of a claim must be analyzed, not in a vacuum, but in light of: (i) the content of the particular application disclosure, and (ii) the teachings of the prior art, and (iii) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. See, for example, *In re Marosi,* 710 F.2d 799, 218 U.S.P.Q. 289 (Fed. Cir. 1983).

Following this analysis, Applicants point out that, as to the first factor to be considered, the specification is replete with explanations and examples of the intended scope of these terms. The Examiner's attention is drawn to a section of the specification entitled "Preparation of Synthetically or Covalently Modified Nucleic Acid Components" beginning at page 26, line 25. This section teaches that modification of the nucleic acid components of the invention is meant to include: modification/mutation of nucleic acid residues, biotinylation, fluorescent tagging and incorporation of polypeptide nucleic acids. Subsequent parts of this section provide specific descriptions of: primer extension-mediated methods of obtaining mutated "modified" nucleic acid components (see page 27, lines 8-16); methods of obtaining biotinylated "modified" nucleic acid components (see page 27, lines 17-24); methods of obtaining fluorescently-tagged "modified" nucleic acid components (see page 27, lines 25-29); and methods of obtaining synthetic oligonucleotide nucleic acid components that are "modified" to contain polypeptide nucleic acid (PNA) components or other functional groups such as primary amines and sulfhydryls which can be further used for conjugation of haptens, proteins, enzymes or antibodies (see page 27, lines 30-33). Furthermore, in regard to the second factor to be considered, the teachings of the prior art provide guidance to the skilled artisan in interpreting the scope of modifications claimed. For example,
Finally, as to the final factor to be considered, Applicants note that one of ordinary skill in the art at the time the invention was made would appreciate that

Applicants believe the aforementioned amendments and the preceding discussion obviate the Examiner's rejection of claims 1-30 and 42 under 35 U.S.C. §112, 2nd paragraph. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claim Rejections under 35 U.S.C. §102

Claims 1-17, 25-33, and 36-38 have been rejected under 35 U.S.C. §102(b) as being anticipated by Watson et al. (Recombinant DNA (1992) Second Edition, pp. 206-9). In particular, the Examiner has cited Figure 11-14, on page 207 of Watson. Applicants respectfully traverse this rejection, because the cited reference fails to teach every element of the claimed invention, as is required to maintain a novelty rejection under 35 U.S.C. §102(b).

Figure 11-14 of Watson depicts a process for "gene synthesis by ligation of complementary oligonucleotides" in which multiple synthetic oligonucleotides, each consisting of a segment of a

functional gene, are ligated together to reconstitute a single isolated double-stranded DNA molecule that encodes a (single) protein of interest. Thus the Watson reference teaches combining multiple synthetic oligonucleotides which constitute fragments of a functionality-encoding gene sequence. Such fragments do not individually provide independent genetic functions to the resulting vector, but rather combine to provide a single genetic functionality to the vector. In contrast, the method of claim 1 requires that each of at least two nucleic acid components supply "at least one genetic element providing a functionality". Similarly, independent claim 31, as amended, requires linkage of nucleic acid components which encode a functionality such as an origin of replication, a selectable marker or a particular functionality-encoding insert of interest. Furthermore, since claims 2-17, and 25-30 are dependent from claim 1, and since claims 32, 33 and 36-38 are dependent from claim 31, all of the claims cited by the Examiner require the combination of multiple nucleic acid components which each encode a functionality. Accordingly, since the Watson reference fails to teach every element of the pending claims, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C § 102(b).

Claim Rejections under 35 U.S.C. §103

Claims 1-42 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Watson et al. (1992) (pp. 206-209) in view of Goodchild ((1990) Bioconjugate Chemistry, Vol. 1, pp. 165-187), and "Applicant's admissions and in further view of the Stratagene Catalog" for the reasons laid forth in the office action. Applicants respectfully traverse this rejection, because the cited references fail to provide the necessary teachings and motivation to arrive at the claimed invention for the reasons provided below.

The Examiner's attention is drawn to MPEP § 706.02(j) which sets forth three requirements necessary to establish a *prima facie* case of obviousness. These include: a suggestion or motivation, either in the references themselves of in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings; a reasonable expectation of success; and a teaching or suggestion provided by the prior art reference (or references when combined) of all the claimed limitations. The following comments address these requirements of a rejection under 35 U.S.C. § 103(a).

In particular, Watson and Goodchild do not provide the claimed method of combining

multiple genetic functionality-encoding nucleic acids into a single vector. The claimed invention requires that each nucleic acid component provide a distinct functionality. In contrast, the Watson reference fails to teach this aspect of the claimed invention, as was discussed above for the rejection under 35 U.S.C. §102 (b).

Next, the Examiner has cited Goodchild because "Goodchild teaches covalently modified nucleic acids using biotinylation, fluorescent tagging and conjugation of enzymes". In particular the Examiner cites Table VI of Goodchild and "Applicants (admission) that modifications to form products such as PNA and yeast artificial chromosomes 'can be performed by a variety of art known techniques'." Applicants assert that these citations neither teach nor suggest the claimed invention singly or in combination with the Watson reference discussed above. Indeed this citation from the Examiner merely supports the notion that there are methods available for both the chemical derivatization of the nucleic acid components and, furthermore, for the chemical joining of these nucleic acid components. These available methods may be used in conjunction with the method of the present invention. Applicants do not contend that the pending claims are distinguished by novel methods of chemical derivatization and/or chemical joining. While the open language of these method claims would allow for the incorporation of derivatization of the nucleic acid components, such an application is neither required nor a particular distinguishing feature of the claimed invention. Furthermore, the mere fact that there are known methods for joining nucleic acid molecules does not render obvious their use in an otherwise novel methodology for producing combinatorial vector libraries. Still further, these citations by the Examiner do not provide a motivation to alter the teachings of Watson to arrive at the claimed invention. Accordingly, the Goodchild reference and the "Applicants (admissions)," considered alone or in combination with the Watson reference, do not render the claimed invention obvious under 35 U.S.C. §103.

The Examiner has further rejected claims 1-42 under 35 U.S.C. §103(a) over the preceding references and "in further view of the 1988 Stratagene Catalog". In particular, the Examiner states that the "Stratagene (catalog) shows gene characterization kits providing a variety of different reagents....which have been assembled and premixed specifically for a defined set of experiments." The Stratagene catalog reference appears to have been cited specifically to support a rejection of claims 39-41, drawn to kits having reagents for use in the method of the invention. Applicants

have amended claims 39-41 to reflect kits providing multiple nucleic acid components, each of which provides a functionality. Claim 42 has been similarly amended. These amendments serve to further define a preferred embodiment of the claimed invention, but are not meant to limit the scope of the present invention and Applicants preserve the right to claim additional patentable subject matter in related applications.

For the foregoing reasons, Applicants believe that the references cited by the Examiner do not render the claimed subject matter *prima facie* obvious under 35 U.S.C § 103(a). Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited.

If any additional fee is required, we authorize that our Deposit Account No. 06-1448 should be charged.

Respectfully submitted,
FOLEY, HOAG, & ELIOT

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